Guidance for Industry and FDA Reviewers on

Evidence Models for the Least Burdensome Means to Market

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U.S. Department of Health and Human Services
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Center for Devices and Radiological Health
Office of Device Evaluation

Preface

Public Comment

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Guidance for Industry and FDA Reviewers on *Evidence Models for the Least Burdensome Means to Market*

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Guidance for Industry and FDA Reviewers on **Evidence Models for the Least Burdensome Means to Market**

Background and Scope

Introduction

Section 205 of the Food and Drug Administration Modernization Act of 1997 (FDAMA) requires FDA, in consultation with the product sponsor, to consider the "least burdensome" means that will allow appropriate premarket development and review of a product without unnecessary delays and expense to manufacturers. The requirement to consider the least burdensome means applies to both existing statutory paths to market: premarket notifications (510(k)s) and premarket approval applications (including PMAs and PDPs). While FDAMA does not change the standards for premarket review (substantial equivalence to a legally marketed predicate for 510(k)s and "valid scientific evidence" to demonstrate a reasonable assurance of safety and effectiveness for PMAs), it does require the agency to focus its review on information directly relevant to supporting the substantial equivalence or safety and effectiveness of the medical device.

In light of the broad range of therapeutic and diagnostic devices the agency regulates, the agency believes that a process approach is necessary to provide guidance on establishing the least burdensome means to market. FDA recognizes that there are many product development and data collection issues that are device specific. The agency anticipates issuing future guidance on the least burdensome approach that are device specific, as well as updating many of the current general and specific guidances in light of these FDAMA provisions.

Background

To foster a collaborative approach to the implementation of section 205 of FDAMA, the Center for Devices and Radiological Health (CDRH) hosted a meeting with stakeholders on January 4, 1999, to solicit comments and suggestions regarding the least burdensome approach to medical device development and evaluation. CDRH heard formal presentations at that meeting and also received written comments.

This CDRH draft guidance has incorporated, in part, the written proposal dated March 11, 1999 from the "Least Burdensome Industry Task Force" convened by the Health Industry Manufacturers Association (HIMA), comments from the January 4, 1999, stakeholders meeting, and other stakeholder communications.

As a result of the communications with stakeholders, it became clear that there are a number of possible tools that reviewers and sponsors could use to facilitate the process of determining the least burdensome means to market. These include:

- A decision algorithm to determine the need for clinical data
- A check list for the contents of a submission (for reviewers & submitters)

- Submission templates (for some common situations)
- Rapid (web page) access to data in the public domain (e.g., cumulative meta-analysis)
- Rapid (web page) access to current guidances for clinical data and study design options

This guidance addresses the first item in this list, a decision algorithm for determining the need for clinical data, because this issue was of the highest concern to stakeholders. The remaining tools will be evaluated, prioritized, and developed as appropriate. Stakeholders are encouraged to submit their own proposals for the development of these additional tools at any time.

Scope of this guidance

This guidance is designed to help both CDRH reviewers and the medical device industry apply the new provisions of FDAMA. Through this guidance, CDRH intends to establish a general approach for applying the least burdensome provisions that will be applicable to any device application; the guidance does not attempt to establish specific clinical data requirements for any particular type of submission.

The focus of this guidance is application of the FDAMA provisions to clinical data requirements because the input from stakeholders has indicated that the regulated industry is most concerned with FDA's interpretation of these provisions with respect to clinical data.

In addition, as this guidance was being developed, it became clear that it cannot easily be applied to *in vitro* diagnostic devices (IVDs) because of the unique clinical data needs associated with establishing IVD performance. The agency is soliciting comments on applying the least burdensome provisions to data requirements for IVDs.

Applicable statutory provisions & regulations

The following statutory provisions and regulations are relevant to the discussion of the "least burdensome" appropriate means to market:

Section 205 of FDAMA references the concept of "least burdensome" in the following contexts:

- ***For PMAs,*** Section 513(a)(3) (21 U.S.C. 360c(a)(3)) is amended by adding at the end the following:

> (D)(ii) Any clinical data, including one or more well-controlled investigations, specified in writing by the Secretary for demonstrating a reasonable assurance of device effectiveness shall be specified as result of a determination by the Secretary that such data are necessary to establish device effectiveness. The Secretary shall consider, in consultation with the applicant, the **least burdensome appropriate means** of evaluating device effectiveness that would have a reasonable likelihood of resulting in approval.

- Section 513 (a)(3) of the Act (21 U.S.C. 360c(a)(3)) remains unchanged by FDAMA. Under that provision, *the effectiveness of a device* is to be determined on the basis of "well-controlled investigations, including 1 or more clinical investigations where appropriate, . . ." unless there is other sufficient "valid scientific evidence" to determine the effectiveness of the device.

FDA's regulations implementing section 513(a)(3) of the Act establish a hierarchy of valid scientific evidence. Under 21 CFR 860.7(c)(2):

> Valid scientific evidence is evidence from:
>
> - well-controlled investigations,
> - partially controlled studies,
> - studies and objective trials without matched controls,
> - well documented case histories, and
> - reports of significant human experience with a marketed device,
>
> from which it can fairly and responsibly be concluded by qualified experts that there is reasonable assurance of the safety and effectiveness of a device under its condition of use.

- ***For 510(k)s,*** Section 513(i)(1) (21 U.S.C. 360c(i)(1)) is amended by adding at the end the following:

> (D) Whenever the Secretary requests information to demonstrate that devices with differing technological characteristics are substantially equivalent, the Secretary shall only request information that is necessary to making substantial equivalence determinations. In making such request, the Secretary shall consider the **least burdensome means** of demonstrating substantial equivalence and request information accordingly.

General principles

FDA believes that the following principles should be applied by reviewers and sponsors to identify the least burdensome approach to product development and review:

- FDA and sponsors should consider whether the extent of effectiveness data required for premarket approval can be reduced through reliance on postmarket controls.
- FDA reviewers and sponsors should apply guidance documents and standards of identity consistently, and identify the types of data that constitute valid scientific evidence to support regulatory submissions.
- The amount and type of data necessary to support premarket review and approval or clearance should be commensurate with the risk of the device.
- The evidence required to support submissions may vary according to the characteristics of the device, its conditions of use, warnings and other restrictions, and experience with the product.
- FDA and sponsors should encourage communication within FDA, and between FDA and industry, regarding the development of the least burdensome means for evaluating specific medical device submissions.
- FDA reviewers should be proactive in suggesting to sponsors the appropriate valid scientific evidence that appears to strike the optimal balance between timely completion of the submission process and probability of success.

How do we approach a determination of the need for clinical data?

Application of the least burdensome provisions to decisions about the need for clinical data is guided by two primary questions:

- What, if any, device-specific clinical data are needed?
- What is the most appropriate and reasonable way to obtain these data (what strikes the right balance between cost to sponsor and likelihood of success)?

As a result of discussions with stakeholders and within the FDA, the agency has developed an approach to this determination that poses four more specific questions:

1. What information is already known about this medical device for this specific intended use?

2. What additional information can be applied to this device from the data currently available about this and other devices?

3. What further data, in addition to the information identified by the first and second questions, are necessary to provide a reasonable assurance of safety and effectiveness for this device (for a PMA device), or to establish substantial equivalence (for a 510(k) device)?

4. If new clinical data are found to be necessary, then how many patients and what type of study design will have a reasonable likelihood of resulting in data that may support the approval or clearance of the medical device without unnecessary delay or expense?

FDA Model

In this guidance, FDA is presenting a model for assessing the need to develop new clinical data and determining the way in which to develop whatever data may be necessary. The model relies on a consistent "process" approach, rather than a table or another hierarchy. It is designed to be used by both FDA reviewers and industry to develop a way to implement the least burdensome concept as it applies to clinical data requirements across all medical device product lines. A schematic of the model is outlined in Appendix 1.

The model relies on two global questions regarding the need for any type of device-specific clinical data to support premarket submission. The discussion that follows is designed to provide guidance for reviewers and sponsors to arrive at the appropriate answers to these global questions.

Question # 1. Are any new device specific clinical data needed or does available valid scientific evidence support the conclusion that the subject device is reasonably safe and effective, or substantially equivalent to a predicate device, when used as indicated in the target population?

Question # 2. What is the most appropriate and reasonable way to obtain these data? Alternatively one could ask: Is a randomized controlled trial (RCT) the least burdensome means of establishing that the subject device is reasonably safe and effective or substantially equivalent to a predicate when used as indicated in the target population?

> *<u>Important Note</u>: Most medical devices available in the United States are cleared for market by the FDA through the 510(k) process. The vast majority of these devices are found to be substantially equivalent to a predicate device [21CFR 807.92(a)(3)] based upon: 1) a complete design description of the device, and 2) data from*

preclinical testing (bench and/or animal studies). New clinical data are not required in most of these circumstances. Therefore, for the vast majority of medical devices, the answer to Question 1 is "yes," the available valid scientific evidence was adequate.

How to answer the questions

Question # 1. Does available valid scientific evidence support the conclusion that the subject device is reasonably safe and effective, or substantially equivalent to a predicate device, when used as indicated in the target population?

To arrive at an answer to Question 1, several points should be considered in order to identify valid scientific evidence that is already available to support the submission. As discussed earlier, this valid scientific evidence can take a variety of forms. Information about the technology of the device from bench testing and data from animal studies are valid scientific evidence that can in part or in whole address this question. Valid clinical scientific evidence includes evidence from well-controlled investigations, partially controlled studies, studies and objective trials without matched controls, well-documented case histories, and reports of significant human experience with this or closely related devices. Whenever such evidence is available, it may be used to establish completely or support in part the safety and effectiveness or substantial equivalence of the device under review. The existence of such evidence may eliminate the need for the sponsor to generate clinical data or may reduce the number of patients or simplify the appropriate design of any additional trials that are necessary.

Points to consider:

The device and the use environment

- What is the device?
- What does it do?
- What is the principal of operation?
- What is the appropriate (necessary) use environment (support facilities)?

The indication and the claim

- What is the target population (i.e., what patient population is intended to benefit)?
- What disease is being treated or diagnosed in the target population?
- What are the appropriate patient inclusion and exclusion criteria for the use of the device?
- What are the known or potential risks to the patient?
- What are the anticipated benefits to the patient?

Our current knowledge of the interaction of the disease/condition and the product

- How well is the physiology/pathophysiology understood?
- How well is the mechanism of action of the device understood?
- What do we already know about the technology/device?
- What do we already know about its use in this patient population/Indication?

Relevance and applicability of the clinical data

Is the device with which it was developed:

- One in which the technology and mode of action are well understood and comparable to these aspects of the device under consideration?
- Intended to provide the same diagnostic or therapeutic intervention for the same disease state/condition and patient population?
- Used in a patient population that is adequate to represent the population to be indicated for the device under consideration? Consider age, gender, severity of disease, co-morbid conditions, duration of therapy, outcome measures.

Regarding the data, what is:

- the effect size (measured benefit) of the treatment in these studies?
- the variability of the data developed; e.g., standard deviation of the results, confidence interval around the data?
- the impact of patient factors on effect size; e.g., age, gender, disease severity?
- the effect size that is clinically meaningful in this population for this disease?

Do the data:

- contain sufficient descriptions of the device, target patient population, procedure including details of device use, follow-up and safety and effectiveness endpoint for the stated indication?
- provide patient accounting information for all screened and enrolled patients?
- include validated direct or surrogate outcome measures for safety and effectiveness (e.g., clinical and radiographic))? Or, are appropriate surrogate outcome measures reported?
- describe an appropriate length of follow-up?
- have an appropriate number of repeated measurements?

Based on the answers to these questions, does the accessible existing data support a finding of substantial equivalence or provide reasonable evidence of safety and effectiveness for the new device under consideration**? If the existing data, including the accessible clinical data, are not sufficient to answer yes to Question 1, then the issues raised in Question 2 need to be considered**.

<u>Important Note:</u> The answer to Question 1 may change over time. For a given medical device type, the need to rely on device-specific clinical data tends to decline over time due to many factors, including the following:

1) improvement in the preclinical assessment technology (increasing experience, greater precision, and wider acceptance, e.g., FDA recognition of standards);

2) increase in the understanding of the relevance of non-clinical data (increased ability to anticipate clinical response from preclinical performance); to understand linkage between non-clinical performance and some clinical endpoints)

3) accumulation of clinical data/knowledge (public domain or belonging to this sponsor);

Examples of how such a transition from a process that requires new manufacturer or model-specific clinical data to one where such data are not routinely required are presented in Appendix 2.

Question # 2. What is the most appropriate and reasonable way to obtain these data? Alternatively one could ask: Is a randomized controlled trial (RCT) the least burdensome means of establishing that the subject device is reasonably safe and effective, or substantially equivalent to a predicate, when used as indicated in the target population?

Stakeholders have tended to focus concerns regarding the least burdensome approach on the decision related to the need for an RCT because they have assumed that an RCT will be more costly in terms of both time and money. However, based on FDA's review experience, this does not always prove to be true. A major advantage of the RCT design is the assurance that confounding factors, such as selection biases, will not be a problem because of the randomization. If there is no randomization then there is a greater need to check for potential confounding factors, hence potentially more burden in validation.

There are many ways to develop valid clinical data. Each trial design presents its own level of burden for data development and evaluation. Approaches to the development of clinical data that are less burdensome in terms of the number of studies, the number of patients, or that rely on non-concurrent comparators, may, in fact, lead to greater burdens in terms of analysis, model validation, or historical data validation.

Depending on the availability of data from previous studies of this device and previously studied similar devices in comparable populations, the questions below may be easy or hard to answer. The difficulty that may be faced in arriving at reliable answers to these questions should be considered before making the decision to perform a non-concurrently controlled trial. Where there are few available well-documented studies, where the size of the treatment effect is small and therefore difficult to differentiate from random variation, where the available studies are not based on current knowledge of the disease and evaluation of affected patients, where the data underlying the patient outcomes are not published and are unavailable to the sponsor, or where the published studies did not provide sufficient patient follow-up, it may be less burdensome overall for the sponsor to perform a concurrently controlled trial.

For these reasons FDA believes that the sponsors also should ask themselves if a concurrently controlled, and where needed, a randomized trial might not be the most straightforward and least burdensome way to support market entry. These queries should investigate whether the patient might be his or her own control in the study, whether there are objective outcomes that have been validated in sufficient trials to allow for uncontrolled studies, whether the patient population of interest has no alternative treatment option and the natural history of the disease is sufficiently well-understood to provide a control for the new intervention. They should also consider if there are biases that might arise in patient selection that could impact the trial if patients are not randomized on entry, if there is a risk of bias in the representation of the entire affected population if the study is not concurrent and perhaps randomized, if the size of the trial can be lessened if the outcomes measures are controlled and consistently applied.

Points to consider:

Is a concurrent controlled study needed?

Are there potential sources for historical comparator data?

- published (peer reviewed) articles;
- publicly supported (NIH, DOD, …) research results;
- previous (PMA or 510(k)) data owned by or accessible to the sponsor;
- patient registries.

How can the comparison be made?

- matching of patients individually from an appropriately comprised large registry (caveats include completeness of the data set, e.g., are all relevant factors which may impact on outcomes captured in a standardized fashion, and assurance that other factors over time may not have impacted natural history, e.g., improvements in supportive care, early diagnosis),
- use of predefined objective performance criteria (OPC) with or without adjustment for individual study (based on patient population baseline characteristics).

Are there potential biases or confounding factors that would make the use of historical data problematic?

- Are there differences in patient populations, standard of care, physician skill and training, methods of data generation, and/or collection and evaluation?
- If differences exist, can we quantify their effects?

Based on the answers to the question of whether a concurrent controlled study is needed, one may identify an already available valid comparator and use that data as the control for the data to be developed for the specific device. If, based on the answers to the questions, a valid comparison is not possible, then a concurrently controlled trial may be needed.

Is randomization necessary (i.e., is it the least burdensome design) to prevent/reduce bias, allow for direct comparison with an established device?

There are several ways to approach this question. What is needed to answer the question is a combination of what specific data need to be developed for the subject device and what biases other study designs might introduce. Bias issues have to do with assessing differences in study populations and understanding the impact of variation in patient populations on the outcome measures of interest in the study of the subject device; determining the appropriate duration of follow-up and applying it to both active and control populations; and understanding how the reliability of the measures being used impact the expected variation in data to be obtained in the trial. What follows is a set of questions that can be used to address these issues.

Study outcome measures

- What will be measured?
- When (how often) will measurements be repeated?

- Who will do the measuring and what training will they receive?
- Can surrogate measures be used in place of primary outcome measures?

Duration of patient follow-up

- How long must patients be followed after treatment in order to establish durability of effect and safety?
- Can statistical or design features shorten the follow-up period for some or all subjects?

Other considerations:

After the appropriate comparator and the type of trial to be conducted are identified, the focus should move to specific issues of trial design. There are additional aspects of trial design that also have different levels of burden and need to be assessed. The following questions are presented to help identify issues to be considered.

The method of analysis and reporting

- Will the Bayesian method or the frequentist approach be used?
- What will be the primary analyses?
- How will covariates be considered?
- How will interactions be addressed?
- What defines study success (safety, effectiveness)?

Study monitoring

- Will an independent clinical events committee (ICEC) be used?
- Will an independent data monitoring committee (IDMC) be used?
- Will there be interim looks at the endpoints (discrete or sequential design)?

Post-approval potentials and needs

- What amount and type of data can be developed after device clearance or approval?

Alternative Approaches

Other processes for arriving at the least burdensome pathway that has a reasonable likelihood of resulting in approval are sure to emerge from further deliberations. This is not a situation where there is only one right way to evaluate the utility of existing data.

One example of an alternative approach has been proposed by the "Least Burdensome Industry Task Force" convened by the Health Industry Manufacturers Association (HIMA). HIMA's model builds off an understanding of basic preclinical data types and the hierarchy of clinical data in 21 CFR 860.7. The premise of this model is that FDA should limit the type and amount of data

requested of the sponsor until a decision has been reached that types of data that are less burdensome to gather cannot address relevant questions. Although conceptually consistent with the FDA model presented here, the practical impact of applying this approach would require that data that is lower on the hierarchy of valid scientific evidence be fully developed and reviewed before a decision could reliably be made to proceed to the next higher level. FDA believes this approach would likely lead to the delay of market entry for many devices, an increase in the number of rounds of review required to assess each level of data, and therefore, more burden to both the industry and FDA.

FDA would appreciate comments on the HIMA model (available in Appendix 3).

Conclusion

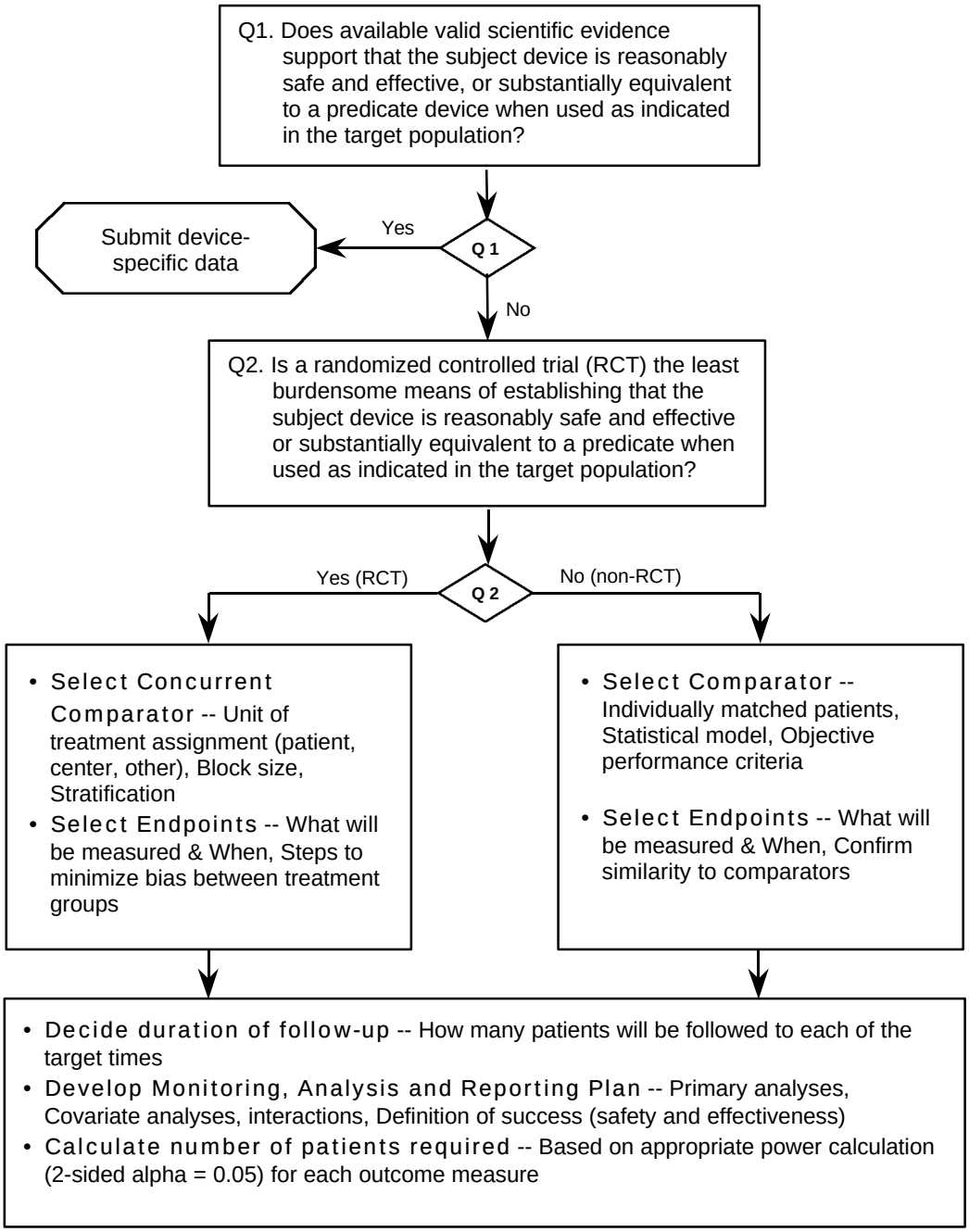
The challenge of section 205 of FDAMA is to develop an efficient model of medical device development and review that will allow safe and effective products to be developed and marketed to consumers without unnecessary delay and expense to manufacturers. Our goal is to provide a process model for reaching a decision about the need for clinical data and the type of clinical data that are the least burdensome means to support successful premarket review.

The agency views this draft guidance as a first step toward developing a useful process model. We encourage our reviewers and other stakeholders to play an active role in refining the model by testing its assumptions. One approach is to apply the model to device-specific examples. Appendix 2 provides two such examples and we invite stakeholders to evaluate additional specific devices.

FDA believes that new device-specific guidances to complement this model can be developed using the same target questions outlined in this document. We encourage the regulated industry to use their expertise and experience developing medical devices to draft those specific guidances for FDA review. In addition, we invite our colleagues in the FDA and other stakeholder to assist in prioritizing the development of other tools, such as those listed on page 1 of this document, that reviewers and sponsors can develop and use to implement the least burdensome provisions of FDAMA.

Appendix 1

Evidence Model Decision Schematic



Appendix 2

Reduction of Clinical Data – Examples

We examined some situations where the industry and the agency have already agreed to reduce the device-specific clinical evidence requirements in the development of a medical device and indication. Discussion of these examples provides specific instances of how reliance on clinical data was reduced or eliminated.

In the first example, the answer to Question 1 changed from "No" to "Yes".

Question # 1. Are any new device specific clinical data needed or does available valid scientific evidence support the conclusion that the subject device is reasonably safe and effective, or substantially equivalent to a predicate device, when used as indicated in the target population?

Metal stents for malignant biliary obstruction (Example 1)

Expandable metal stents for management of malignant biliary obstruction are in Class II, and cleared originally via 510(k) premarket notification. Expandable metal biliary stents were found to be "substantially equivalent" to biliary catheters (Product Code: FGE), and therefore are included under the classification of 21 CFR §876.5010 (Biliary catheter and accessories):

(a) **Identification**. A biliary catheter and accessories is a tubular flexible device used for temporary or prolonged drainage of the biliary tract, for splinting of the bile duct during healing, or for preventing stricture of the bile duct. This type of device may include a bile collecting bag that is attached to the biliary catheter by a connector and fastened to the patient with a strap.

(b) **Classification**. Class II.

During the middle to late 1980's, data from bench testing and from clinical studies were needed to support substantial equivalence decisions for these devices. As the familiarity with these devices increased, the reliance on clinical data for the substantial equivalence decision decreased. There appeared to be a good correlation between the results of the various bench tests on the expandable metal stents and the clinical results observed in patient use for the specific Indication for Use of the palliative treatment of malignant biliary obstruction. This trend was observed in the first 10 submissions, and has continued to the present, with more than 40 cleared 510(k) submissions for expandable metal biliary stents. Currently, data from clinical studies are not required unless concerns regarding safety and effectiveness are raised by bench testing results that are significantly different from that observed for the predicate device.

The suggested bench testing has been described in the following FDA guidance as follows:

"Bench testing of biliary stents is required [shouldn't say required in guidance—where does quote end?] to establish substantial equivalence. The following tests are recommended:

A. Deployment Testing. This test is performed to verify the reproducibility of stent placement using the deployment system. The stent is usually deployed in a tube having similar characteristics (i.e., size, lubricity) to the bile duct and the results should demonstrate ease of deployment and the accuracy of stent placement. Test results should be provided for the largest and smallest diameter stents that are to be marketed.

B. Expansion Force Testing. This test is performed to measure the force exerted by the stent as it expands. The predicate device should be tested with the same apparatus and the results should be provided for both the proposed and the predicate devices. These test results should be provided for every diameter stent that is to be marketed.

C. Compression Force Testing. This test is designed to measure the force required to compress the stent once it is expanded. Similar to the expansion force test, the predicate device should be tested with the same apparatus and the results should be provided for the proposed and the predicate devices. These test results should be provided for every diameter stent that is to be marketed.

D. Dimensional Testing. This test is performed to verify the reproducibility of the stent length and diameter after deployment. These test results should be provided for every diameter stent that is to be marketed.

E. Corrosion Testing. This test is performed to establish the compatibility of the stent materials with the corrosive environment in the biliary tree. The stent should be in contact with simulated bile for a period of time that is representative of the implantation time of the device. After exposure to the simulated bile, the tensile strength of the stent material should be measured and compared to the untreated stent. Visual inspection of the stent using microscopy should also be performed. Accelerated exposure conditions may be used (e.g., elevated temperatures), however, a rationale should be provided on how the accelerated conditions are representative of the actual clinical use conditions.

F. Balloon Performance Testing. If the deployment mechanism uses a balloon inflation catheter, balloon burst strength data should be provided. In addition, data should be provided on the times for balloon inflation and deflation. These test results should be compared to the results of the predicate device in the same test apparatus.

G. Stent Deformation Testing for balloon expandable stents. If the deployment mechanism uses a balloon inflation catheter, data should be provided to demonstrate that the mechanical integrity of the stent is unaffected when the balloon is expanded to its burst point.

H. Tensile Strength Testing. This test should be performed for any deployment system that includes components that are bonded or welded.

If the technology and/or materials of the stent and/or deployment system are significantly different from the predicate device, animal testing may be required. Clinical data may also be required, depending upon the extent of the difference between the proposed and predicate devices. There are no performance standards or special controls for biliary stents at this time" (Guidance for the Content of Premarket Notifications for Metal Expandable Biliary Stents, February 5, 1998, www.fda.gov/cdrh/ode/bistent.html).

Factors that contribute to the reduction of the need for clinical data

This change in data requirements was the result of a number of factors:

1) The natural history of the disease treated in the Indications for Use is well known. In this case, there is a large body of published literature on the clinical course of patients with malignant biliary obstruction, and the adverse events which are expected to be observed in patients who have received palliative treatment.
2) There have been a large number of similar devices cleared for the same Indication for Use. In this case, there have been over 40 expandable metal biliary stent submissions cleared under 510(k).
3) The FDA guidance document has helped provide a standard approach to the bench testing of expandable metal stents.

Cautionary factors

What other factors need to be considered as a result of these changes in data requirements?

1) Although the FDA guidance document has helped provide a standard approach to the bench testing of expandable metal stents, there is still variability in how the specific bench test is performed by the different 510(k) sponsors. This variability in testing methods would be a problem if the sponsor did not perform the bench testing on both the new biliary stent, as well as the predicate stent. If the bench test results of the new stent are similar to those of the predicate stent, then supporting clinical data is not required. The degree of difference allowed between the new stent and the predicate is based upon the past experience with that specific bench test, and how a significantly higher or lower test value could affect performance characteristics.
2) If the 510(k) for a new expandable metal biliary stent was submitted to the FDA as a "Special 510(k)", then the FDA reviewer would not be able to analyze the actual data from bench testing of both the new stent and the predicate. Since there are no industry wide standard for the performance of these various bench tests for expandable metal stents, there would be no standard to which to declare conformity.

Prosthetic replacement heart valves (Example 2)

In this second example, the answer to Question 2 changed from "Yes", where a RCT was needed, to "No" (non-RCT clinical data).

Question # 2. What is the most appropriate and reasonable way to obtain these data? Alternatively one could ask: Is a randomized controlled trial (RCT) the least burdensome means of establishing that the subject device is reasonably safe and effective or substantially equivalent to a predicate when used as indicated in the target population?

Cardiac valve prostheses are mechanical or biologic (allograft or heterograft tissue) replacement devices for significantly malfunctioning heart valves. The various types of valve prostheses differ in their performance characteristics, durability and reported rates of patient adverse events. Even the current generation of valve prostheses cannot exactly duplicate the durability and hemodynamic effectiveness of the natural valve. Prosthetic valves can be either mechanically constructed, or fashioned from biologic tissues. Mechanical construction achieves a durable

structure, but is associated with a higher adverse event rate when compared to tissue valves, which is often attributed to concurrent anticoagulation use. Tissue prostheses offer better hemodynamic performance, and often reduce or eliminate anticoagulation requirements. However, these benefits come with a sacrifice in valve durability.

Valvular heart disease has been treated surgically for 50 years, with prosthetic valve replacement available for the past 30 years. Since the passage of the Medical Device Amendments in 1976, the marketing of prosthetic valves in the U.S. has required PMA approval, supported by a controlled clinical trial demonstrating at least equivalence to a legally marketed valve prosthesis serving as a concurrent control.

Since 1976, there have been improvements in prosthetic valve engineering, mathematical modeling and pre-clinical testing. These advances have allowed for a more reliable characterization of valve function, hemodynamic properties, and durability. Currently, there is considerable cumulative experience on prosthetic valve clinical performance, given the implantation rate of approximately 200,000 devices/year.

Based upon this vast technological and clinical experience, a Heart Valve Guidance Document was developed in 1994 which outlined criteria for the pre-market evaluation of cardiac valve prostheses. Input for this guidance was obtained from both clinicians and manufacturers at a public workshop. The participation of professional organizations such as the American Association for Thoracic Surgery, and the Society of Thoracic Surgeons, as well as the FDA's Circulatory System Devices advisory panel was also critical to this process.

As outlined in this Heart Valve Guidance, while recognizing the need for prosthetic valve clinical trials, consideration was given to relying on non-concurrent or historical controls in the appropriate situations, as an alternative to a concurrent controlled trial. In addition, the Ad Hoc Liaison Committee for Standardizing Prosthetic Heart Valve Morbidity of the Society of Thoracic Surgeons and Association for Thoracic Surgery listed the following as the most significant adverse events related to prosthetic valves: thromboembolism, valve thrombosis, hemorrhage, valve leak, and endocarditis. A linearised rate recorded as events per patient-year, designated Objective Performance Criterion (OPC), was computed for each of these significant adverse events. These computations were derived from the peer reviewed literature, covering a ten year period. This analysis covered the experience of 10,000 patients who received prosthetic valves and provided clinical data equivalent to 45,000 patient-years.

The Heart Valve Guidance recommended that any proposed clinical trial design be powered to achieve a 95% confidence that the adverse event rate for the lowest OPC not exceed twice the control value. For a clinical trial with a 80% power, with an expected Poisson distribution, 800 prosthetic valve years follow-up of implants would be required.

It was suggested that patient experience be distributed equally among the anatomical implant sites and that at least three centers provide one-year follow-up on no less than100 devices, 50 at each site. Both mortality and structural valve failure should be captured for all prosthetic valve implantations.

Clinical effectiveness for prosthetic valve replacement is based upon the assessment of changes in the implanted patient's New York Heart Association Classification of cardiac symptomatology, in

addition to changes in the patient's hemodynamic performance as measured by echocardiographic evaluations.

Enabling Factors

1) Long history with consistent device performance reported in peer reviewed literature.
2) Well developed bench, mathematical and *in vivo* performance evaluation
3) High quality non-invasive clinical objective monitoring (echo vs. catheterization)
4) Continuing professional society surveillance of the reliability of valve prostheses
5) Periodic international professional society meetings[1] dedicated to the evaluation of valve prostheses.

Cautionary factors

It has been repeatedly observed that even relatively minor changes to an approved prosthetic valve can influence its safety profile. Given this evidence, clinical evaluation of such changes is still required. Product claims of a new indication for use, or a new specific benefit, such as affecting prosthetic valve effectiveness or durability, would require a clinical trial with an appropriate study design to support the specific device claim.

In the evaluation of outcome measures not included among the five OPCs (hemodynamic performance and survival), results are compared to FDA selected peer reviewed reports for similar devices, i.e., mechanical or tissue valves.

[1] Proceedings of the VII International Symposium for Cardiac Bioprostheses, Barcelona, Spain, June 13-15, 1997. Ann Thorac Surg 1998; 66(6 supp): S30-269.

Appendix 3

Health Industry Manufacturers Association Proposal

Development History

12/2/98 .... Bruce discusses the issue with CDER staff & outlines project
12/7/98 .... Circulatory System Device panel considers coronary stents
12/15/98 .. Bert & Dan meet at PhRMA to consider philosophy
1/4/99 ..... Least Burdensome Paths to Market: Industry-FDA meeting
1/6/99 ..... Adequacy of a single trial for NDAs– R O'Neill lecture
1/14/99 .... DCRND presents version 2 in ODE rounds
1/20/99 .... Susan and Dan develop version 3 for Henney briefing
1/27/99 .... Greg and Dan work over model concepts
1/29/99 .... Jane Henney briefing, Bruce, Susan, Kathy Zoon, Jerry Donlon, …
2/10/99 .... Dan inserts Gene Pennello's comments
3/4/99 ..... meeting with Bob Temple – emphasized the need for examples
3/9/99 ..... First meeting of the Least Burdensome team
3/23/99 .... Least Burdensome meeting # 2
3/18/99 .... We received industry task force proposal from HIMA (dated 3/11/99)
4/2/99 ..... Susan roughs out Guidance plan
4/8/99 ..... Dan & Susan complete draft, version 6.0 to the team
4/14/99 .... Least Burdensome meeting # 3
4/19/99 .... Dan includes m/u Roxolana, Jerome, Ashley, Gene, John, Brian, Mark by 4/18, version 6.1
4/21/99 .... Roxy & Dan include suggestions received from Laksmi, Bob, by 4/220, version 6.2
4/24/99 .... Dan changes approach from 3 questions to 2 questions
4/28/99 .... Dan & Wolf complete revisions per Roxy & SXA 4/26 m/u, version 6.3a
4/29/99 .... Dan does final polish with SXA suggestions, version 6.3a to LB team, DDs, Ods
5/3/99……Brian replaces Dan, reviews version 6.3a with SXA with "Plain English" approach (6.3b)
5/7/99……Brian and SXA receive input from LSK (versions 7.0, 7.1)
5/12/99…..Brian, SXA, LSK provide additional revisions (version 8.0)
5/14/99…..Further revisions/update of Table of Contents/Summary; Brian, SXA, LSK (version 8.1)

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